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Pharmacokinetics of meloxicam in mature swine after intravenous andoral administration

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Running title: Pharmacokinetics of meloxicam in mature swine

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Abbreviations

AUC_{extrap}, Percent of the AUC extrapolated; AUC_{INF}, Area under the curve extrapolated to infinity; Cl, Plasma clearance; Cl/F, Cl per fraction of the dose absorbed; C0, Concentration extrapolated to time 0 using log-linear regression of the first two time points; C_{MAX}, Maximum plasma concentration; T_{MAX}, Time to C_{MAX}; T ½ λz, Terminal half-life; λz, Terminal rate constant; MRT, Mean residence time extrapolated to infinity; Vss, Volume of distribution at steady state; Vz, Volume of distribution, area method; Vz/F, Vz per fraction of the dose absorbed; MAT, Mean absorption time; F, Fraction of the dose absorbed; COX, Cyclo-oxygenase; HPLC-MS, High pressure liquid chromatography and mass spectrometry detection; PK, Pharmacokinetic; NSAIDS, Non-steroidal anti-inflammatory drugs; IV, Intravenous; IM, Intramuscular; PO, Per os (by mouth)

Abstract

The purpose of this study was to compare the pharmacokinetics of meloxicam in mature swine after intravenous (IV) and oral (PO) administration. Six mature sows (mean bodyweight ± standard deviation = 217.3± 65.68 kg) were administered an IV or PO dose of meloxicam at a target dose of 0.5 mg/kg in a cross-over design. Plasma samples collected up to 48 hours post-administration were analyzed by high pressure liquid chromatography and mass spectrometry (HPLC-MS) followed by non-compartmental pharmacokinetic analysis. Mean peak plasma concentration (C_{MAX}) after PO administration was 1070 ng/ml (645-1749 ng/ml). T_{MAX} was recorded at 2.40 hour (0.50-12.00 hours) after PO administration. Half-life (T ½ λ_z) for IV and PO administration was 6.15 hours (4.39-7.79 hours) and 6.83 hours (5.18-9.63 hours) respectively. The bioavailability (F) for PO administration was 87% (39-351%). The results of the present study suggest that meloxicam is well absorbed after oral administration.

Keywords

Swine, meloxicam, pharmacokinetics, NSAIDs, oral bioavailability, pig

Introduction

Over the past decade there has been increased awareness from the public on issues related to farm animal welfare. More specifically, concern over procedures that inflict pain upon pigs (i.e. castration, tail docking) and lack of pain relief available during these procedures has been highlighted as major concerns from the public (Guatteo et al., 2012; Coetzee, 2013a; Millman, 2013). Non-steroidal anti-inflammatory drugs (NSAIDs) including ketoprofen, carprofen, flunixin meglumine and meloxicam are common analgesics used to manage animal pain and are labeled

for pain control for livestock in Canada and some European Union countries (Coetzee, 2013b). However there are currently no drugs approved for use in swine and specifically labelled to provide pain relief in the United States (FDA 2010).

Meloxicam is a member of the oxicam class with anti-inflammatory, analgesic and antipyretic properties (Friton et al., 2003; Hirsch et al., 2003). Meloxicam is highly protein bound (95-99%), demonstrates good systemic absorption (Busch et al,. 1998) and may be a good candidate for pain mitigation in swine. To identify the optimal dose regimen for pain management, the pharmacokinetics of a drug must be determined. Pharmacokinetic (PK) parameters for meloxicam have been evaluated in several species including cattle (Coetzee et al., 2009; Mosher et al., 2012; Malreddy et al., 2013), small ruminants (Shukla et al., 2007; Ingvast-Larsson et al., 2010; Wasfi et al., 2012; Krueder et al., 2012; Stock et al., 2013), horses (Toutain et al., 2004; Sinclair et al., 2006), exotics (Divers et al., 2010) and companion animals (Lees et al., 2013; Lehr et al., 2010). There have been two peer-reviewed articles published on Meloxicam PK in swine (Fosse et al., 2008; 2010). However, these studies evaluated meloxicam PK properties in pre-pubertal swine age 14-23 days and neither study evaluated oral bioavailability (F) of meloxicam. The purpose of this study was to compare the pharmacokinetic parameters of IV and oral meloxicam PK in mature swine and to determine the oral bioavailability.

Methods

This study was approved by the Institutional Animal Care and Use Committee at Iowa State University.

Animals and housing

Six healthy multiparous commercial cross-bred Newsham cull sows (mean bodyweight ± standard deviation = 217.3± 65.68 kg) were used for this study. Sows were housed in individual pens with a concrete floor with and rubber mat (2.4 m length x 2 cm height x 1.4 m width). Sows were provided *ad libitum* access to water via one nipple drinker (Trojan Specialty Products Model 65, Dodge City, KS) and hand-fed a custom mixed diet free of antibiotics or medications composed of corn, soybean meal and soy hulls, designed to meet or exceed nutrient requirements for sows. Approximately 1.8 kg of feed was fed at 0800 and 0.45 kg of feed was fed at 1600 hours onto a raised concrete step (55 cm length x 55 cm in width x 24 cm). Matrix (Altrenogest formulation; Intervet/Schering-Plough, Milsboro, DE- Dose: 6.8 ml-15 mg) was added to one kg of feed daily to prevent estrus cycle initiation.

Twenty-four hours before study commencement, sows were moved to individual gestation stalls (2.1 m length x 0.6 m width) with nonslip rubber flooring. Sows had access to the same type of nipple drinker previously described for the pen, and remained in their stalls for a total of 72 hours while on trial (on trial defined as sows receiving drug and having blood collected). Sows on trial, regardless of administration route, received the same ration and were fed on the same schedule as follows: **Day 1**: 0.9 kg at 5:00 (three and half hours prior to oral drug administration), 1.4 kg at 12:30 and .45 kg at 17:00; **Day 2**: 2.3 kg at 8:30 and 0.45 kg at 17:00. Lights were on a 12:12 light dark cycle (light hours [0600 and 1800]). Feed schedule was different on trial days due to trial schedule and blood collection time-points. Attitude, appetite, and blood collection sites of sows were monitored twice daily during each study period. Sows were assessed for immediate adverse reactions to drug administration including demonstrating signs of sedation, seizures, vomiting, diarrhea or respiratory compromise. Post-mortem necropsies were not conducted and clinical signs of melena were not evaluated.

Study design

A cross-over design study (Navidi, 2008) was conducted over two rounds such that all sows received each administrative route. Sows were blocked by body weight and treatments were randomly assigned to sows within a block (three sows per block) with three sows allocated to each administration route for the first round. A10-day washout period was chosen as it was greater than 89 times the half-life reported in swine (Fosse et al., 2008; $T_{1/2\,b}$: 2.7 hours). Sows were weighed 20 hours prior to study initiation and these weights were used to calculate drug dosages.

In the first round, three sows were administered an intravenous injection of meloxicam (**IV-M**) at 0.5 mg/kg (Loxicam 5 mg/ml; Norbrook Pharmaceuticals Worldwide, Station Works, Newry, Ireland # 1155103) as a single bolus injection into an indwelling auricular vein catheter using techniques described by Pairis-Garcia and colleagues (2014). Three sows received meloxicam per os (**PO-M**) at 0.5 mg/kg (Meloxicam 15 mg/tablet; Zydus Pharmaceuticals USA Inc, Pennington, New Jersey #MM5058). Tablets were mixed with approximately 24 g of sugar cookie dough (sows had been previously trained using cookie dough as a positive reinforcement), divided into three, 8 gram round balls, and administered in a clean feeding bowl. In the second round, this process was repeated so that all sows received both meloxicam routes. For oral administration, the dose was rounded to the nearest whole tablet. For intravenous administration, the dose was rounded to the nearest half milliliter. The experimental unit was the individual sow (n = 6/treatment).

Blood collection

All blood samples (9.0 mL/sample) were collected via the jugular vein using a 25.4 mm 16 gauge hypodermic needle (Air-Tite Products, Virginia Beach, VA, USA) and 12 ml luer lock syringe (TycoHealth Care, Mansfield, MA, USA). During blood collection, sows were manually

restrained using a pig snare. Blood was collected from sows receiving IV-M at 0.05, 0.1, 0.17, 0.33, 0.5, 1, 2, 4, 8, 12, 16, 24, 36 and 48 hours after drug administration. Blood was collected from sows receiving PO-M at 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, 36, and 48 hours after PO administration. A baseline sample was collected 20 hours prior to drug administration for both routes. Samples were immediately transferred to a sodium heparin 10 ml blood collection tube (BD Vacutainer, Franklin Lakes, NJ, USA) and remained on ice for no longer than 150 minutes prior to centrifugation for 10 minutes at 1,500 *g*. Collected plasma was placed in cryovials and frozen at -70 °C until analysis.

HPLC/MS analysis of meloxicam concentrations

Plasma meloxicam concentrations were determined using high-pressure liquid chromatography (Surveyor MS Pump and Autosampler, Thermo Scientific, San Jose, CA, USA) with mass spectrometry (TSQ Quantum Discovery MAX, Thermo Scientific, San Jose, CA, USA). Plasma samples, spikes (0.20 ml) and the internal standard (piroxicam; 10 µL 40ng/ml) were treated with 20 µL of 30% perchloric acid. Samples were vortexed for 5 seconds and centrifuged for 20 minutes at 2,500 x *g* to precipitate the sediment. The supernatant (~80 µL) was pipetted into a glass insert containing 120 µL of 1.9% ammonium hydroxide in 25% aqueous acetonitrile and fitted to an injection vial. The injection volume equaled 12.5 µL. Two mobile phases utilized were as follows: A. 0.1% formic acid in water B. 0.1% formic acid in an acetonitrile at a flow rate of 0.250 mL/min. The mobile phase began at 15% B with a linear gradient to 95% B at 7 minutes, which was maintained for 1.5 minutes, followed by a re-equilibration to 15% B. Separation was achieved with a solid-core c18 column (KinetexXB -C18, 100 mm×2.1 mm, 2.6 µm particles, Phenomenex, Torrance, CA, USA) maintained at 40°C. Piroxicam eluted at 4.85 minutes and meloxicam at 5.95 minutes. Four SRM transitions were monitored for meloxicam

and three SRM transitions were used with the internal standard, piroxicam. The quantifying ions for meloxicam were 72.99, 88.01, 114.99, and 140.98 m/z and 77.97, 94.98, and 120.98 m/z for piroxicam. Sequences consisting of plasma blanks, calibration spikes, QC samples, and swine plasma samples were batch processed with a processing method developed in the Xcalibur software (Thermo Scientific, San Jose, CA, USA). The processing method automatically identified and integrated each peak in each sample and calculated the calibration curve based on a weighted (1/X) linear fit. Plasma concentrations of meloxicam in unknown samples were calculated by the Xcalibur software based on the calibration curve. Results were then viewed in the Quan Browser portion of the Xcalibur software. The standard curve in swine plasma was linear from 0.005 to 10.0 μg/mL. The coefficient of determination (R squared) exceeded 0.995 and all measured values were within 15% of the actual values with most of the values less than 5% difference from the actual values. The accuracy of the assay for meloxicam in swine plasma was 99 ± 3% of the actual concentration while the coefficient of variation was 5% determined on 4 sets of replicates for each of the following concentrations: 0.015, 0.15, and 1.5 μg/mL. The limit of quantitation (LOQ) for this assay was determined to be 0.005 ug/mL, while the limit of detection (LOD) was 10-fold lower than that at 0.0005 ug/mL.

Pharmacokinetic analysis

Pharmacokinetic analyses for plasma meloxicam concentrations over time were performed with computer software (WinNonlin 5.2, Pharsight Corporation, Mountain View, CA, USA) and analyzed using non-compartmental methods (Gibaldi and Perrier, 1982).The parameters included the area under the curve from time 0 to infinity (AUC_{INF}) using the linear trapezoidal rule, percent of the AUC extrapolated to infinity (AUC_{EXTRAP}), plasma clearance (Cl), first-order rate constant

(λ_z), terminal half-life ($T_{½}$ λ_z), apparent volume of distribution at steady state (Vss), apparent volume of distribution of the area (Vz), mean residence time extrapolated to infinity (MRT), and mean absorption time (MAT). The maximum plasma concentration (C_{MAX}) and the time to maximum plasma concentration (T_{MAX}) were observed for PO administration. The concentration at time 0 (C0) was calculated by log-linear regression using the first two time points after IV administration. The AUC_{EXTRAP} was the percent of the AUC extrapolated to infinity. The range of the λz was determined by visual inspection of the plasma profile and determined by linear regression of time and natural log (ln) of the plasma concentration. The Vz was determined using the following equation:

$$Vz = \frac{Dose}{\lambda z * AUC_{INF}}$$

The Vss was determined with the following equation:

$$Vss = MRT * Cl$$

The F was estimated with the following equation:

$$F = \frac{\frac{AUC\ (PO-M)}{Dose\ (PO-M)}}{\frac{AUC\ (IV-M)}{Dose\ (IV-M)}}$$

The MAT with the following equation:

189 $$MAT = MRT\ (PO - M) - MRT\ (IV - M)$$

190 Given that pharmacokinetic parameters data follow a log-normal distribution, geometric statistics
191 are more appropriate summary descriptors and have been presented in this study.
192
193 **Results**

194 No adverse effects (sedation, seizures, vomiting, diarrhea**,** or respiratory compromise) from the
195 sow were observed following IV or PO meloxicam administration and drug levels were below the
196 limit of detection on baseline days. Two samples were excluded for IV administration at the 24
197 hour time point due to unclear labeling with unclear sow identification. Two samples were
198 excluded for IV administration and PO administration at the 48 hour time point as samples were
199 below LOQ. A 13.9% variation within samples was detected as compared to the internal standard
200 response across all samples.

201 Figure 1 and 2 presents the individual plasma profiles for IV-M and PO-M administered at 0.5
202 mg/kg (actual mean dose: IV: 0.50 mg/kg; range: 0.49-0.50 mg/kg; PO: 0.49 mg/kg; range 0.47-
203 0.51 mg/kg).

204 Table 1 summarizes the calculated PK for IV-M and Table 2 summarizes the calculated PK for
205 PO-M.

206 **Discussion**

207 In this study, we compared the PK parameters of IV and PO meloxicam in mature swine
208 and determined the oral bioavailability. Although meloxicam PK properties were previously
209 evaluated at 0.4 mg/kg in swine (Fosse et al., 2008; 2010), the authors completed this work using

younger, immature pigs (14-23 days of age) and did not evaluate PO-M administration. Hence, the present study is novel because we determined these parameters, including oral, in mature pigs using a different route of administration and dose. .

The MRT of 4.26 hour and Cmax at 5705 ng/ml were numerically greater than results reported by Fosse and colleagues, 2008 (MRT: 3.5 ± 0.3 h; Cmax: 3277 ± 250 ng/ml) although Vss was similar at 0.16 l/kg (Fosse et al 2008; Vss: 0.19± 0.02 l/kg) and the Cl was slower at 0.63 ml/min/kg (Fosse et al 2008; Cl: 1.01 mL/kg/min). Half-life was also different when compared to previous results from Fosse and colleagues (2010; T ½ λz 2.6h), Norbrook Laboratories (2014; T ½ λz 2.5h) and laboratory pigs (T ½ λz 2.48h; European Agency for the Evaluation of Medicinal Products (EMA), 1999), although similar to results for mice and mini-pigs (EMA, 1999; T ½ λz 4-6h). Although the cause of these differences is unknown, several factors may have contributed to the numerical differences. Since these were separate studies, direct comparison should always be cautious as differences in study design such as routes of administration, fed or fasted animals, sample collection times, analytical method (including limit of quantification, sensitivity, and specificity), drug formulations, environmental factors and pharmacokinetic analyses differences could all contribute to some of the perceived differences. Differences in pharmacokinetic parameters from our study compared to previously published results may also be due to differences in age, genetics, weight or additional unknown differences between study populations. Although it is often assumed that young animals always have slower drug metabolism / elimination than adults, this is not the case. In Beagle dogs for example, puppies aged 5-20 weeks have shorter half-lives and more rapid clearance of caffeine than adult dogs (Tanaka et al., 1998). Similarly the half-life is shorter in puppies aged 3-30 weeks and the clearance is more rapid of trimethadione (a nonspecific metabolism substrate) than adult dogs

233 (Tanaka et al., 1998). Mosher and colleagues (2012) demonstrated differences in half-life when
234 comparing pre-ruminant calves and ruminant calves administered meloxicam by gavage (pre-
235 ruminant calves dosed via gavage: T ½ λz 40.0h; ruminant claves dosed via gavage: T ½ λz
236 29.9h). In addition, breed or strain differences may also contribute due to genetic differences
237 (polymorphisms) in metabolism, but to the authors' knowledge, genetic polymorphisms or
238 extensive studies of the effects of age on drug metabolism in pigs have not been reported.

239 Previous studies have demonstrated excellent bioavailability for meloxicam ranging
240 between 72-100% F when administered to horses and ruminants (Calves: Coetzee et al., 2009;
241 Goats: Ingvast-Larsson et al., 2010; Horses: Toutain et al., 2004; Sheep: Stock et al., 2013;
242 Camels: Wasfi et al., 2012; Llamas: Krueder et al., 2012). Our study demonstrated oral F at 87%
243 (range 39-350%). The lower range in F coincides with previous studies conducted in sheep
244 (Stock et al, 2013; 40%) and llamas (Kreuder et al, 2012; 48%). As there are no other studies
245 assessing bioavailability in sows, it is unclear if variability in F should be expected in sows, or
246 other factors such as feeding regimen or drug formulation influenced this outcome.

247 When assessing the upper range of F at 350% a possible explanation for the elevated F
248 from this particular sow may be due to slow absorption. As the drug was administered orally we
249 can rule out slow absorption due to administration complications such as hemorrhage, injection
250 into fascial plane or seroma formation. However, drug absorption by oral administration can be
251 influenced by local damage at the site of absorption (gastrointestinal tract), decreased blood flow
252 and variation in stomach contents (Maddison et al, 2008). Gastric ulcers, intestinal torsions,
253 volvulus and proliferative enteropathy are common problems seen in swine (Thomson and
254 Friendship, 2012). Compromised gastric mucosa due to disease may result in decreased blood

flow to the affected site, prolonged retention of feed and decrease in total surface area resulting in potentially slower drug absorption (Page and Maddison, 2008). As sows enrolled on trial were purchased from a group of commercial cull sows, chronic gastrointestinal disease or compromise may be possible. Necropsies of sows were not performed therefore gastrointestinal tract status is unknown and may have played a role in variations seen with oral meloxicam F. Therefore, it may be more appropriate to use the median F at 69% or estimated F without this sow (67%) as a better indicator of true F.

Conclusions

The pharmacokinetic profile of oral meloxicam described in this study including the high relative bioavailability support clinical evaluation of this compound for management of pain in sows. Meloxicam may be both cost effective and require little additional training for administration on farm.

Competing interests

The authors state that there are no competing interests related to the present study**.** Dr. Coetzee has been a consultant for Intervet-Schering Plough Animal Health, Boehringer-Ingelheim Vetmedica and Norbrook Laboratories Ltd. Dr. KuKanich has been a consultant for Bayer Animal Health, Central Life Sciences, Pfizer Animal Health, and Procyon Pharmaceuticals. Dr. Millman has been a consultant for or has received funding from Boehringer-Ingelheim Vetmedica, Bayer Animal Health and Pfizer Animal Health. Dr. Johnson and Dr. Stalder has been a consultant for or have received funding from Boehringer-Ingelheim Vetmedica, Pfizer Animal Health and Elanco

Animal Health. Dr. Karriker has been a consultant for or has received funding from Boehringer Ingelheim Vetmedica and Bayer Animal Health.

Authors' contributions

JFC and LAK conceived the study, participated in the design and coordination and assisted with the drafting the manuscript. MPG participated in data compilation, sample processing, design and coordination and drafted the manuscript. AKJ provided funding participated in the design and coordination, and aided in interpretation of the data and drafting the manuscript. KJS and STM participated in the study design, coordination and drafting the manuscript. BK performed the pharmacokinetic analysis and assisted with the data interpretation. LWW performed the plasma drug analysis on all samples. All authors read and approved the final manuscript.

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